Urol Res (2011) 39:123–127
DOI 10.1007/s00240-010-0309-y

ORIGINAL PAPER

Bioavailability of magnesium from different pharmaceutical formulations

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Received: 6 May 2010 / Accepted: 2 September 2010 / Published online: 23 September 2010

Abstract Magnesium is suggested to reduce intestinal oxalate absorption and to act as an inhibitor of calcium oxalate crystallization in the urine. However, previous studies have shown only minimal increase in urinary magnesium excretion following oral magnesium supplementation, possibly due to its low bioavailability. This study was performed to examine the bioavailability of magnesium from two different pharmaceutical formulations of magnesium oxide (MgO). Thirteen healthy male volunteers (22–31 years) were recruited from university students and staff, and all completed the study. During the baseline phase, subjects collected two 24-h urines while on their usual diet. Throughout the control and test phases, the subjects consumed a standardized diet calculated according to the recommendations. During the test phases, subjects received two magnesium preparations in a cross-over procedure. With each preparation, MgO-capsules and MgO-effervescent tablets, 450 mg magnesium was supplemented. On the control day and the two test days, fractional urine collection was performed and six corresponding blood samples were taken. In the follow-up phase, subjects continued to take the respective preparation while on their usual diet and collected 24-h urines weekly. With standardized conditions, urinary magnesium excretion increased by 40% after ingestion of the effervescent tablets, and by only 20% after intake of the capsules. The results indicate better bioavailability of magnesium from the effervescent tablets than from the capsules. This may be attributed to the fact that the tablets have to be dissolved in water before ingestion so that magnesium becomes ionized, which is an important precondition for absorption.

Keywords Magnesium oxide · Urinary magnesium excretion · Serum magnesium · Hypomagnesuria · Bioavailability · Magnesium supplementation

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Introduction

Hypomagnesuria is a common finding in calcium oxalate urolithiasis. A study in recurrent calcium oxalate stone formers revealed hypomagnesuria (urinary magnesium excretion <3 mmol/24 h) in 19% of patients on their usual diet [1, 2]. Increased urinary magnesium concentrations have been demonstrated to reduce nucleation and growth rates of calcium oxalate crystals most likely due to the formation of soluble complexes with oxalate [3, 4]. Moreover, magnesium is suggested to reduce oxalate absorption by binding exogenous oxalate in the intestine [5–7].

While several studies have demonstrated beneficial effects of supplementation of magnesium oxide or hydroxide on calcium oxalate stone formation [8–10], others were unable to confirm these findings [11–13]. However, in previous studies, urinary magnesium excretion has either not been reported at all [9, 11, 13] or was found to increase only marginally following oral supplementation of magnesium oxide [14], possibly due to its low bioavailability. These findings may explain the insufficient evidence for the recommendation of magnesium salts for the treatment of calcium oxalate stone disease [15].

The bioavailability of orally ingested magnesium depends on the type of magnesium salt and its administration form. Although information about the bioavailability of different magnesium preparations is available [16–19],

comparative studies on the bioavailability of magnesium from different pharmaceutical formulations are lacking. Due to its low cost, magnesium oxide is often used as supplement. The aim of the present study was therefore to compare the bioavailability of two pharmaceutical formulations of magnesium oxide, i.e., capsules and effervescent tablets, under short-term (24 h) and long-term (4 weeks) administration of a daily dosage in healthy subjects under controlled standardized conditions. With a consistent magnesium balance the magnesium absorption can be reliably determined from the renal magnesium excretion [16, 20, 21].

Subjects and methods

Subjects

Thirteen healthy male subjects with a mean age of 26.6 years (range 22–31 years) were recruited from university students and staff. In order to obtain a homogenous group, only men were recruited for the study. Due to male predominance in urolithiasis, male instead of female subjects were chosen. Each subject had a normal physical examination and normal findings from multiparameter urine test strips (Combur^9-Test, Boehringer, Mannheim, Germany) measuring pH, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, leucocytes, and blood. No subject had a prior medical history of significant diseases. The subjects took no medication or vitamin and/or mineral supplements during the study. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Bonn University Medical Center. All participants gave their informed consent prior to their inclusion in the study.

Study design

The study design is presented in Table 1. During the baseline phase (phase I) volunteers collected two 24-h urines once weekly while on their usual diet. The control and test period was divided into two phases of 4 days each (phases II and III), separated by a 4-day wash-out phase. Throughout the control and test phases, the subjects received a standardized balanced mixed diet, calculated according to the dietary recommendations [22]. The energy and nutrient composition of the standardized diet is summarized in Table 2. The diet, providing 404 mg magnesium per day, allowed for saturation of the subjects' magnesium pools. After a few days of adaptation the standardized diet, i.e., the daily constant intake of prescribed foods and fluids, leads to a steady state of metabolism so that urinary values reach constant levels [23].

Table 1 Study design

Phase I		Phase II				Wash-out phase	Phase III				Phase IV				
Baseline phase		Control phase			Test phase 1		Control phase			Test phase 2	Follow-up phase				
Week 1	Week 2	Day 1	Day 2	Day 3	Day 4	4 days	Day 1	Day 2	Day 3	Day 4	Week 1	Week 2	Week 3	Week4	
Usual diet		Standardized diet			+ 450 mg Mg Cross over	Usual diet	Standardized diet			+ 450 mg Mg Cross over	Usual diet + 450 mg Mg				
24-h urine	24-h urine	24-h urine	24-h urine	Urine fractions Serum	Urine fractions Serum		24-h urine	24-h urine	24-h urine	Urine fractions Serum	24-h urine	24-h urine	24-h urine	24-h urine	
Control	Control	Adaptation		Control	Test		Adaptation			Test	Test	Test	Test	Test	

Table 2 Energy and nutrient composition of the standardized diet during the control and test phases

Energy (kcal)	2,533
Energy (kJ)	10,612
Protein (g)	96
Fat (g)	107
Carbohydrates (g)	290
Calcium (mg)	823
Magnesium (mg)	404
Potassium (mg)	2,500
Sodium (mg)	4,100

During test phases 1 and 2, respectively, the two magnesium preparations were applied in a randomized cross-over procedure at 8 a.m. as follows: In test phase 1, seven subjects received the capsules and six subjects received the effervescent tablets. In test phase 2, the preparations were changed. With each preparation, 450 mg magnesium was supplemented. Fractional urine collection was performed on day 3 of the control phase (control day) and during test phases 1 and 2 (test days), respectively. Urine was collected in the following fractions: 8 a.m.–10 a.m., 10 a.m.–noon, noon–2 p.m., 2 p.m.–6 p.m., and 6 p.m.–8 a.m. (next morning). Corresponding blood samples were taken at 8 a.m., 10 a.m., noon, 2 p.m., 6 p.m., and 8 a.m. (next morning). During the 4-week follow-up phase (phase IV), subjects returned to their usual diet but continued to take the respective preparation and collected 24-h urines weekly.

Sample preparation and analyses

Urine samples were collected in polyethylene bottles containing thymol in isopropanol as a preservative. The samples were kept refrigerated at 4°C during collection. For the determination of magnesium urine samples were acidified with hydrochloric acid. Aliquots were then kept frozen at −20°C until analysis. Analysis of urine included urine volume and the concentration of creatinine as a marker for completeness of 24-h urine collection. Magnesium concentration was measured in serum and urine by atomic absorption spectrophotometry (CV 0.3%).

Statistical analysis

Differences between urinary parameters of the corresponding days of each phase were assessed by the two-tailed Wilcoxon matched pairs signed rank test. P values <0.05 were considered statistically significant. The third day of phase II and the fourth day of phases II and III, respectively, were considered control and test days since by then conditions of steady state were reached. Moreover, 24-h urine collections during the follow-up phase were compared with baseline 24-h urine collections. Statistical analyses were performed using SPSS 11.0 (SPSS, Chicago, IL, USA).

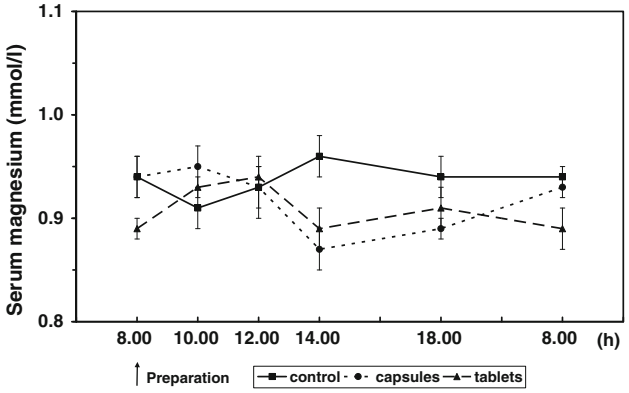

Fig. 1 Circadian rhythm of serum magnesium (mmol/l) of 13 healthy male subjects on the standardized diet receiving magnesium oxide capsules, magnesium oxide effervescent tablets or no supplement (control) (mean ± standard error)

Results

Serum magnesium concentrations on the control and the two test days are shown in Fig. 1. All serum magnesium concentrations remained consistently within the normal range. No significant differences were observed at any time.

The circadian rhythm and the 24-h urinary magnesium excretion on the control and the two test days are reported in Table 3 and demonstrated in Fig. 2. After ingestion of the capsules the renal magnesium excretion was higher in each fraction compared with the control. However, the differences were not statistically significant. After intake of the effervescent tablets, fractional magnesium excretion increased significantly from 10 a.m. onwards compared with the control fractions and differed significantly from the capsules in the second, third, and fourth fractions. With regard to the 24-h urinary magnesium excretion a significant increase was observed only with intake of the effervescent tablets, but not the capsules.

The long-term administration of the effervescent tablets under usual dietary conditions led to a significant increase in urinary magnesium excretion throughout the entire follow-up interval of 4 weeks, with the exception of the second week, compared with baseline phase (Table 4). The long-term intake of the capsules resulted in a significant increase in urinary magnesium excretion only in the first week of the follow-up phase compared with the baseline phase.

Discussion

The courses of the serum magnesium concentrations indicate that although magnesium supply strongly increased following administration of each preparation, the serum

Table 3 Urinary magnesium excretion per hour (mmol/h) and per 24-h (mmol/24 h) of 13 healthy male subjects on the standardized diet receiving magnesium oxide capsules, magnesium oxide effervescent tablets or no supplement (control)

Time (h)	8.00–10.00	10.00–12.00	12.00–14.00	14.00–18.00	18.00–8.00	24-h
Control						
M	0.210	0.240	0.185	0.205	0.160	4.340
SE	0.025	0.025	0.010	0.013	0.012	0.230
Capsules						
M	0.240	0.285	0.240	0.220	0.203	5.210
SE	0.035	0.035	0.020	0.018	0.028	0.385
Tablets						
M	0.230	0.395*,°	0.275*,°	0.318*,°	0.224*	6.100*
SE	0.025	0.070	0.030	0.025	0.031	0.559

* Sign. versus control; °sign. versus capsules, $p < 0.05$

M mean; *SE* standard error

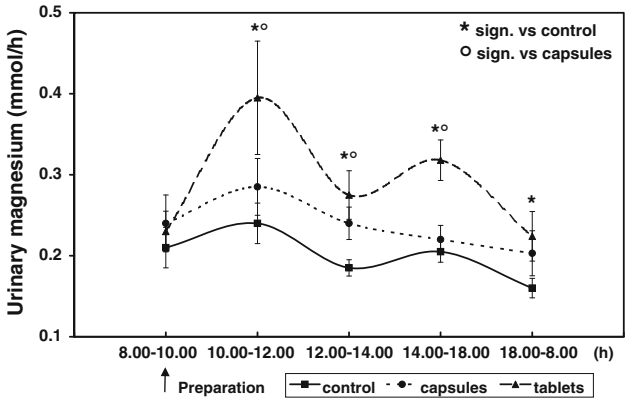

Fig. 2 Circadian rhythm of urinary magnesium excretion (mmol/h) of 13 healthy male subjects on the standardized diet receiving magnesium oxide capsules, magnesium oxide effervescent tablets or no supplement (control) (mean ± standard error)

Table 4 Twenty-four hours urinary magnesium excretion of 13 healthy male subjects on their usual diets without supplement (baseline phase) or receiving magnesium oxide capsules or magnesium oxide effervescent tablets (follow-up phase)

	Baseline phase			
	Week 1			Week 2
Control				
M	4.64			4.22
SE	0.70			0.52
	Follow-up phase			
	Week 1	Week 2	Week 3	Week 4
Capsules				
M	6.72*	5.86	6.37	6.18
SE	1.12	0.76	0.98	0.73
Tablets				
M	6.12*	7.27	7.44*	9.48*
SE	1.06	1.93	0.62	1.81

* Sign. versus baseline phase, $p < 0.05$

M mean; *SE* standard error

level remained within the normal range due to homeostatic balance of counterregulative processes, with renal excretion being the major process involved.

To characterize the availability of magnesium, the magnesium input and output had to be compared. On the control day, the subjects were provided with 404 mg magnesium per day (=16.6 mmol/day) with the standardized diet and an average of 4.34 mmol or 105.5 mg magnesium per day were excreted, which corresponds to 26% of the supply. Magnesium bioavailability from the standardized diet is in accordance with previous findings in healthy subjects. With an average magnesium intake from a balanced mixed diet, magnesium absorption has been found to be approximately 20–30% of the intake [20, 23, 24].

With each preparation, 450 mg magnesium was supplemented so that the whole supply amounted to 854 mg magnesium per day. After ingestion of the capsules, 5.21 mmol or 126.7 mg magnesium per day was excreted, corresponding to an increase of about 20% compared with the control day. Supplementation with the effervescent tablets resulted in an average excretion of 6.1 mmol or 148.3 mg magnesium per day, which is a 40% increase as compared with the control day. When referred to the magnesium intake of 450 mg with each preparation, bioavailability of magnesium was 4.7% from the capsules and 9.5% from the effervescent tablets. The low absorption observed for magnesium oxide capsules corresponds to that observed in prior studies of magnesium oxide bioavailability [16, 19]. However, the increase in magnesium absorption from magnesium oxide effervescent tablets indicate that bioavailability of magnesium from the effervescent tablets is comparable to that of the organic magnesium salts, i.e., magnesium

lactate, aspartate, amino-acid chelate, and citrate [16, 19]. Long-term administration of magnesium confirmed the higher bioavailability of magnesium from effervescent tablets compared with capsules.

The results indicate that although the same amount was supplemented with each preparation, with the effervescent tablets the increase in magnesium excretion was twice as that obtained with the capsules. As a consistent magnesium balance can be assumed under standardized conditions, the results indicate a much better availability of magnesium from the effervescent tablets compared with the capsules. Effervescent tablets have to be dissolved in water prior to ingestion. Apart from magnesium oxide, effervescent tablets contain sodium carbonate, sodium bicarbonate, and excess citric acid as auxiliary substances. During solution CO_2 production, acidic pH value and excess citric acid achieve complete solubility of the magnesium salt, so that magnesium becomes readily ionized. This is an important precondition for absorption. The better availability of the magnesium of the effervescent tablet can be attributed to this particular pharmaceutical formulation.

The limited bioavailability of magnesium oxide from the capsules could explain the poor response to this magnesium salt in stone-forming patients [11, 13]. Controlled clinical trials are needed to evaluate the efficacy of a marked increase in urinary magnesium excretion on calcium oxalate stone formation.

Conflict of interest The authors declare that they have no conflict of interest.

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